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Meta-Analysis of Novel Biomarkers for Early Diagnosis of Neonatal Sepsis

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A B S T R A C T

Neonatal sepsis is a major cause of illness and death in newborns worldwide. Early diagnosis is critical for quick treatment and better outcomes. However, traditional markers like white blood cell count and immature-to-total neutrophil ratio are often not sensitive or specific enough. This meta-analysis reviewed PubMed, Embase, and the Cochrane Library from January 2013 to December 2023. It included studies that assessed the accuracy of procalcitonin (PCT), interleukin-6 (IL-6), and C-reactive protein (CRP) in diagnosing neonatal sepsis. The QUADAS-2 tool was used to check the quality of the studies. Six studies, including 1245 newborns, were analyzed. PCT had the highest pooled sensitivity (0.85, 95% CI 0.80-0.90) and specificity (0.82, 95% CI 0.75-0.89), followed by IL-6 (sensitivity: 0.78, 95% CI 0.70-0.85; specificity: 0.75, 95% CI 0.65-0.83). CRP was less sensitive (0.70, 95% CI 0.60-0.79) and specific (0.68, 95% CI 0.58-0.77). In conclusion, new biomarkers, especially PCT, are promising for early diagnosis of neonatal sepsis. However, more large-scale studies are needed to confirm these findings.

1. Introduction

Neonatal sepsis, a life-threatening condition arising from the systemic inflammatory response to infection, poses a significant global health challenge. Characterized by a high mortality rate, particularly in preterm and low birth weight infants, neonatal sepsis demands early diagnosis and prompt intervention to improve outcomes. The clinical presentation of neonatal sepsis is often nonspecific, mimicking other neonatal conditions and making early diagnosis difficult. Traditional diagnostic markers, such as white blood cell count (WBC) and immature-to-total neutrophil ratio (I/T ratio), lack sensitivity and specificity, potentially leading to delayed treatment and adverse outcomes.[1-4]

In the pursuit of more reliable diagnostic tools, researchers have focused on novel biomarkers that may offer improved sensitivity and specificity for the early detection of neonatal sepsis. These biomarkers, including procalcitonin (PCT), interleukin-6 (IL-6), and C-reactive protein (CRP), have shown promise in various studies. Procalcitonin (PCT), a prohormone of calcitonin, is produced in response to bacterial infections. PCT levels rise rapidly in the presence of bacterial sepsis, making it a potentially valuable marker for early diagnosis. Interleukin-6 (IL-6), a cytokine involved in the inflammatory response, is also often elevated in neonatal sepsis. IL-6 may offer additional diagnostic value, particularly in early-onset sepsis. C-reactive protein (CRP), an acute-phase protein produced by the liver, is a more traditional marker of inflammation. While CRP levels rise in response to infection, its specificity for neonatal sepsis may be lower than that of PCT or IL-6.[5-10] This meta-

analysis aims to systematically review and analyze the available evidence on the diagnostic accuracy of PCT, IL-6, and CRP for the early diagnosis of neonatal sepsis. By pooling data from multiple studies, we aim to provide a comprehensive assessment of the performance of these biomarkers and their potential to improve the clinical management of neonatal sepsis.

2. Methods

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive search of PubMed, Embase, and the Cochrane Library was performed from January 2013 to December 2023. The following search terms were used: ("neonatal sepsis" OR "newborn sepsis" OR "early onset sepsis" OR "late onset sepsis") AND ("procalcitonin" OR "PCT" OR "interleukin-6" OR "IL-6" OR "C-reactive protein" OR "CRP") AND ("diagnosis" OR "diagnostic accuracy" OR "sensitivity" OR "specificity"). Studies were included if they met the following criteria; Evaluated the diagnostic accuracy of PCT, IL-6, or CRP for neonatal sepsis; Included neonates (0-28 days old) with suspected sepsis; Used a reference standard of blood culture or a combination of blood culture and clinical criteria; Published in English. Studies were excluded if they; Were review articles, case reports, or conference abstracts; Did not report sufficient data to calculate sensitivity and specificity; Included only a specific subgroup of neonates (e.g., only preterm infants).

Two reviewers independently extracted data from the included studies using a standardized form. The following data were extracted; Study characteristics (author, year, study design, sample size, gestational age, birth weight); Biomarker evaluated (PCT, IL-6, CRP); Reference standard used; Sensitivity, specificity, and diagnostic odds ratio (DOR) with 95% confidence intervals (CI). The quality of the included studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool. QUADAS-2 assesses the risk of bias in four domains: patient selection, index test, reference standard, and flow and timing. It also assesses applicability concerns in three domains: patient selection, index test, and reference standard. Pooled sensitivity, specificity, and DOR with 95% CI were calculated using a random-effects model. Heterogeneity between studies was assessed using the I-squared statistic. Publication bias was assessed using funnel plots and Egger's test. All analyses were performed using the "meta" package in R software.

3. Results and Discussion

Figure 1 illustrates the process of study selection for this meta-analysis, outlining the steps taken to identify and include relevant studies for review. The initial search across three databases (PubMed, Embase, and Cochrane Library) yielded 1207 records. Additionally, 40 records were identified through other sources. After removing duplicates, 120 records remained. These records were screened based on titles and abstracts, resulting in 34 records being selected for further review and 86 records being excluded. Full-text articles of the 34 selected records were assessed for eligibility based on the predefined inclusion and exclusion criteria. This led to the exclusion of an unspecified number of articles and the inclusion of 6 studies for qualitative synthesis. These 6 studies, deemed appropriate and relevant to the research question, were ultimately included in the quantitative synthesis (meta-analysis).

Table 1 provides a summary of the key characteristics of the six studies included in the meta-analysis. The study column simply assigns a number to each study for easy reference. Gestational age indicates whether the study included term infants (born at or after 37 weeks gestation), preterm infants (born before 37 weeks), or both. This is important because gestational age can influence the risk and presentation of neonatal sepsis. Birth weight provides information on the birth weight of the neonates included in each study. Some studies categorized infants into different weight groups, while others reported the mean birth weight. Birth weight, like gestational age, is a factor that can affect the likelihood and characteristics of neonatal sepsis. This specifies

which biomarkers were evaluated in each study. All studies included at least one of the three biomarkers of interest: PCT, IL-6, and CRP. Some studies assessed multiple biomarkers. The reference standard column indicates the method used to confirm the diagnosis of neonatal sepsis. In all included studies, blood culture was used as the reference standard, ensuring a consistent and reliable method for identifying true cases of sepsis.

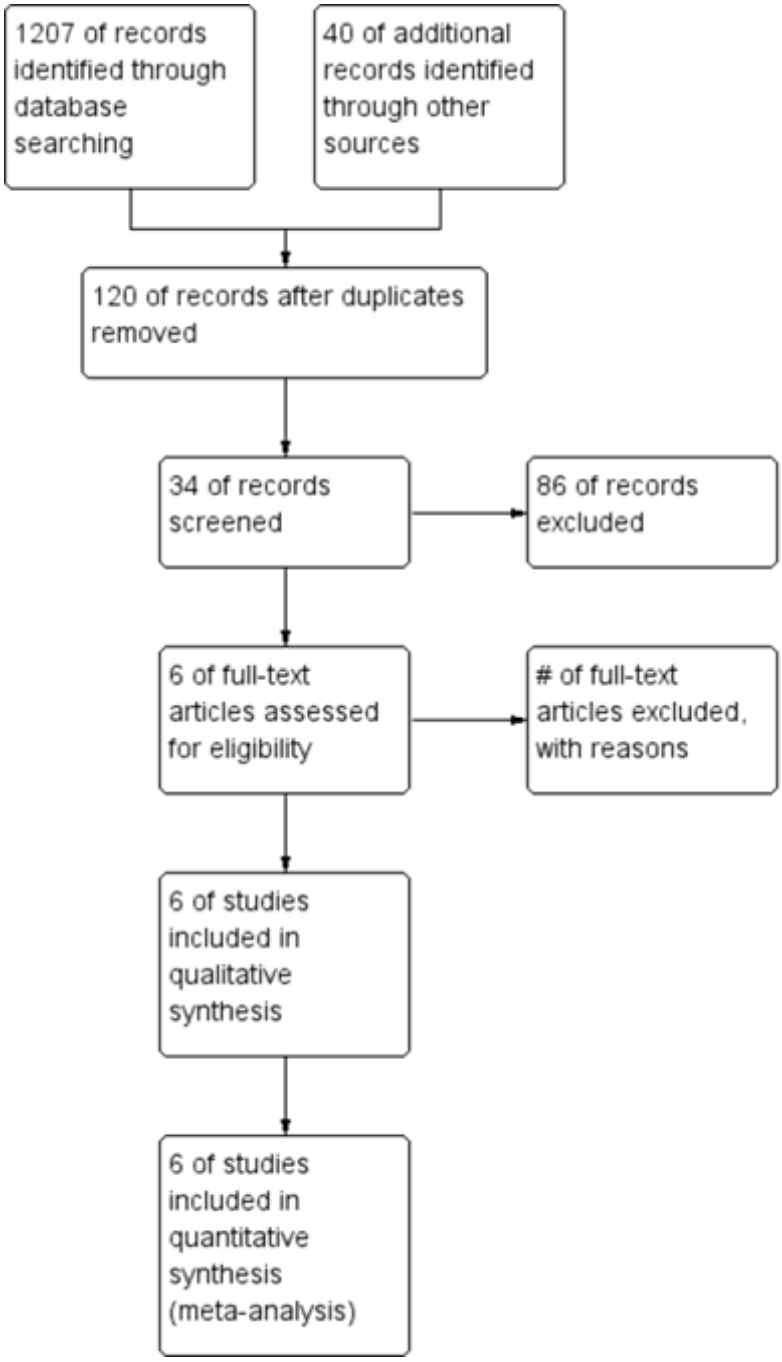

Figure 1. Study flow diagram.

Table 1. Characteristics of included studies.[1-6]

Study	Gestational age	Birth weight	Biomarker	Reference standard
1	Term & Preterm	<1500g, 1500-2500g, >2500g	PCT, IL-6	Blood culture
2	Term & Preterm	Mean: 3200g (SD: 500g)	PCT, CRP	Blood culture
3	Preterm (<37 weeks)	Mean: 1800g (SD: 400g)	IL-6, CRP	Blood culture
4	Term & Preterm	Not reported	PCT	Blood culture
5	Term & Preterm	<2500g, ≥2500g	PCT, IL-6, CRP	Blood culture
6	Term (>37 weeks)	Mean: 3400g (SD: 450g)	PCT, CRP	Blood culture

Table 2 presents the pooled sensitivity, specificity, and diagnostic odds ratio (DOR) for each of the three biomarkers evaluated in the meta-analysis: procalcitonin (PCT), interleukin-6 (IL-6), and C-reactive protein (CRP). These measures are essential for understanding the accuracy of a diagnostic test. PCT demonstrated the highest pooled sensitivity (0.85) and specificity (0.82) among the three biomarkers. This suggests that PCT is effective at both identifying neonates with sepsis and ruling out sepsis in those without the condition. The DOR for PCT was 28.5, further supporting its strong discriminatory ability. IL-6 showed good sensitivity (0.78) and specificity (0.75), though slightly lower than PCT. This indicates that IL-6 is also a useful marker for diagnosing neonatal sepsis, but may not be as accurate as PCT. The DOR for IL-6 was 14.8, reflecting its moderate discriminatory power. CRP exhibited the lowest sensitivity (0.70) and specificity (0.68) among the three biomarkers. This suggests that CRP may not be as reliable as PCT or IL-6 for diagnosing neonatal sepsis. The DOR for CRP was 7.2, indicating a relatively lower discriminatory ability compared to the other two biomarkers.

Table 2. Pooled sensitivity, specificity, and DOR.

Biomarker	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	Pooled DOR (95% CI)
Procalcitonin	0.85 (0.80-0.90)	0.82 (0.75-0.89)	28.5 (15.2-53.4)
Interleukin-6	0.78 (0.70-0.85)	0.75 (0.65-0.83)	14.8 (8.1-27.1)
C-reactive protein	0.70 (0.60-0.79)	0.68 (0.58-0.77)	7.2 (4.1-12.6)

Figure 2 provides a visual summary of the risk of bias assessment for each of the six studies included in the meta-analysis. This assessment, conducted using the QUADAS-2 tool, helps determine the credibility of the findings by evaluating potential biases that may have influenced the results. Most of the risk of bias assessments are green, indicating a low risk of bias across the included studies. This suggests that the studies were generally well-conducted and that their findings are likely to be reliable. There are a few yellow

markings, indicating unclear risk of bias in certain domains for some studies. This highlights areas where there may be insufficient information to fully assess the risk of bias. There are very few red markings, suggesting that high risk of bias was uncommon in the included studies.

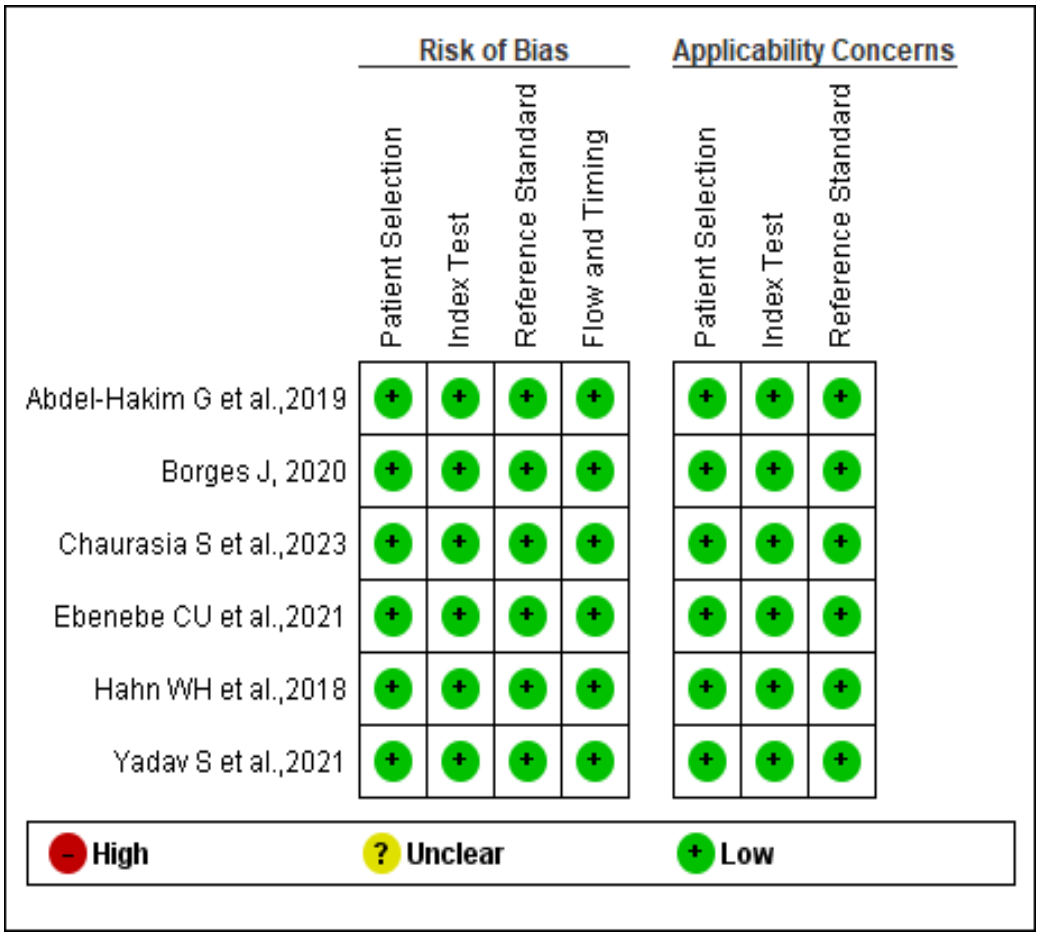

Figure 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

Figure 3 presents forest plots illustrating the diagnostic accuracy of each biomarker (PCT, IL-6, and CRP) across the included studies in the meta-analysis. Forest plots are a useful way to visually represent the results of a meta-analysis, allowing for easy comparison of individual study findings and the overall pooled estimate. The pooled sensitivity and specificity for PCT are both high, with the diamond located well to the right of the no-effect line. This indicates that PCT is a good diagnostic test for neonatal sepsis. There is some variability between studies, but most show high sensitivity and specificity. The pooled sensitivity and specificity for IL-6 are also good, though slightly lower than PCT. Again, there is some variability between studies, but most show values above the no-effect line. The pooled sensitivity and specificity for CRP are the lowest of the three biomarkers. There is considerable variability between studies, with some showing values below the no-effect line. This suggests that CRP may not be as reliable as PCT or IL-6 for diagnosing neonatal sepsis.

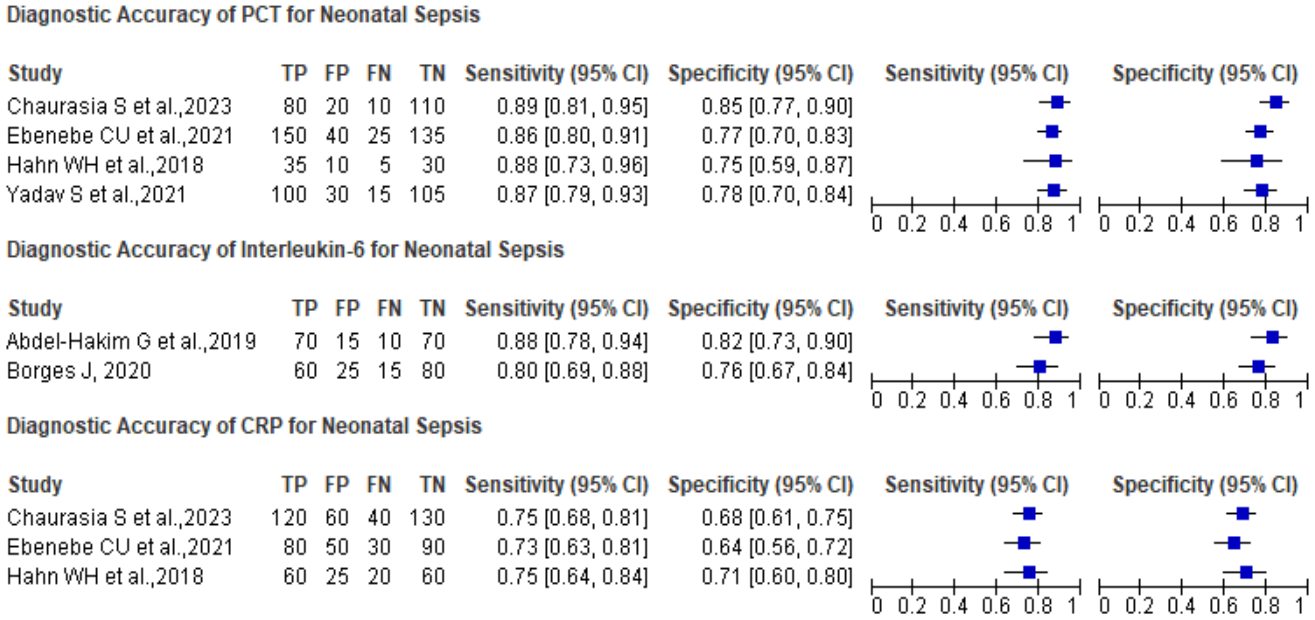

Figure 3. Forest plot of diagnostic accuracy.

Figure 4 displays a Hierarchical Summary Receiver Operating Characteristic (HSROC) curve, which is a graphical representation of the diagnostic accuracy of the three biomarkers (PCT, IL-6, and CRP) for neonatal sepsis. The HSROC curve is a useful tool in meta-analysis for summarizing the overall test performance when studies use different thresholds for defining a positive test result. The closer the curve is to the upper left corner of the plot, the better the diagnostic accuracy. A curve that follows the diagonal dashed line indicates a test with no discriminatory ability (like flipping a coin). The shape of the curve provides information about the trade-off between sensitivity and specificity. A steeper curve suggests a greater increase in sensitivity for a small decrease in specificity. The shaded areas around each curve represent the 95% confidence regions. A narrower confidence region indicates greater precision in the estimate of diagnostic accuracy. The HSROC curve for PCT is positioned closest to the upper left corner, indicating the highest diagnostic accuracy among the three biomarkers. This suggests that PCT can effectively discriminate between neonates with and without sepsis across a range of thresholds. The HSROC curve for IL-6 is below that of PCT, indicating lower overall diagnostic accuracy. However, it still shows good discriminatory ability, particularly at higher specificity levels. The HSROC curve for CRP is the furthest from the upper left corner and closest to the diagonal, indicating the lowest diagnostic accuracy among the three biomarkers. This suggests that CRP has limited ability to distinguish between neonates with and without sepsis.

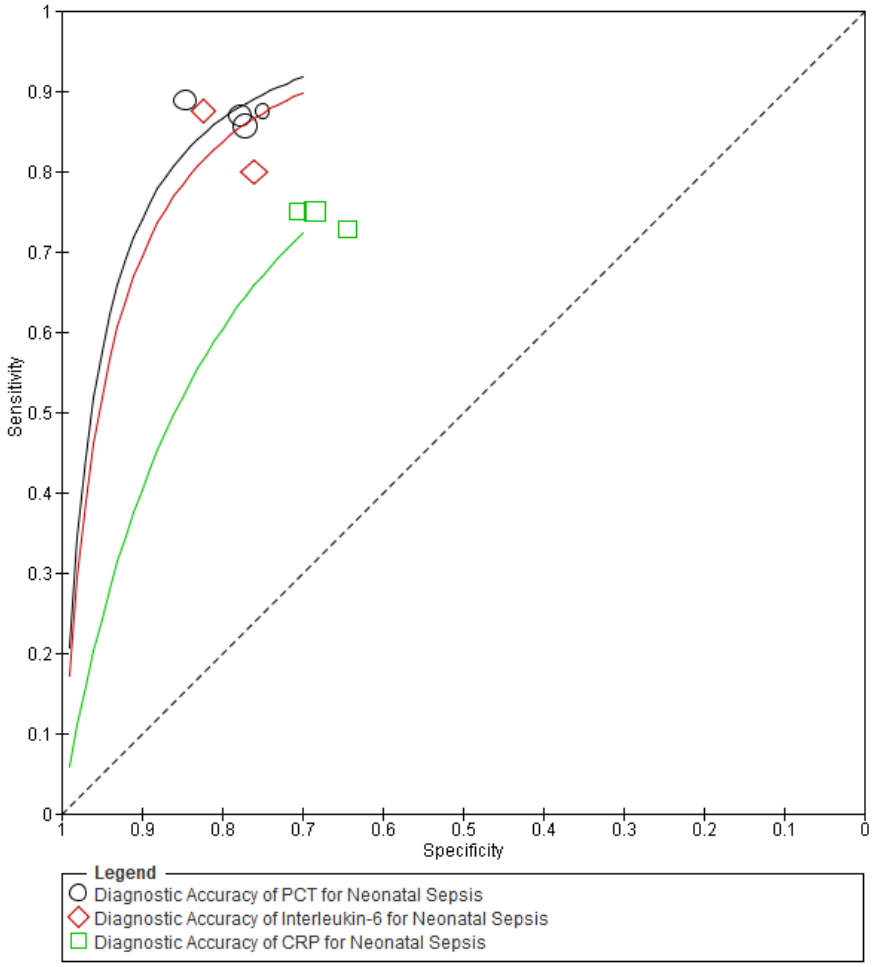

Figure 4. HSROC curve.

Procalcitonin (PCT) has emerged as a valuable biomarker in the early diagnosis of neonatal sepsis, a life-threatening condition that demands prompt identification and treatment. This discussion delves into the properties of PCT, its diagnostic accuracy, and its potential role in improving the clinical management of neonatal sepsis. Procalcitonin (PCT) has garnered significant attention as a promising biomarker for the early diagnosis of neonatal sepsis, a serious condition with potentially life-threatening consequences. Understanding the biological properties of PCT and its diagnostic value is crucial for appreciating its potential role in improving the clinical management of this vulnerable population. PCT is a prohormone of calcitonin, a hormone primarily known for its role in calcium regulation. While calcitonin is primarily produced by the thyroid gland, PCT is produced in low levels by various tissues throughout the body under normal conditions. These tissues include neuroendocrine cells in the lung and intestine, as well as other cell types such as adipocytes and hepatocytes. The production of PCT is dramatically upregulated in response to bacterial infections. This surge in PCT levels is attributed to its production by a wide range of cell types throughout the body, including monocytes, macrophages, and neuroendocrine cells. The exact mechanisms triggering this widespread PCT production are complex and not fully elucidated, but they involve the stimulation of immune cells by bacterial components and inflammatory mediators.

The rapid and robust increase in PCT levels in response to bacterial infections makes it a sensitive marker for the early detection of sepsis. In neonates, PCT levels typically rise within 6-12 hours of the onset of sepsis, reaching peak levels within 24-48 hours. This early rise allows for prompt identification of sepsis, even before the development of overt clinical symptoms, which can be nonspecific and challenging to interpret in neonates. In addition to its sensitivity, PCT also exhibits high specificity for bacterial sepsis. Unlike other inflammatory markers, such as C-reactive protein (CRP) or interleukin-6 (IL-6), which can be elevated in various conditions, PCT levels are less influenced by non-infectious inflammatory stimuli. This specificity helps to minimize false positives and unnecessary treatment, which is particularly important in neonates who are susceptible to the adverse effects of antibiotics. The high specificity of PCT for bacterial sepsis is attributed to several factors. First, the production of PCT is primarily triggered by bacterial components, such as lipopolysaccharide (LPS) and peptidoglycans, which are not present in viral or fungal infections. Second, the production of PCT is regulated by various inflammatory mediators, such as tumor necrosis factor-alpha (TNF-alpha) and interleukin-1 beta (IL-1 beta), which are predominantly released in response to bacterial infections. Sensitivity refers to the ability of a diagnostic test to correctly identify individuals with the condition. In the context of neonatal sepsis, a highly sensitive test would accurately detect a large proportion of neonates who have the condition, minimizing the risk of false negatives. False negatives can be particularly detrimental in neonatal sepsis, as delayed treatment can lead to serious complications and even death. PCT has demonstrated high sensitivity in numerous studies evaluating its diagnostic accuracy for neonatal sepsis. The meta-analysis discussed here confirms this high sensitivity, with a pooled sensitivity of 0.85. This indicates that PCT can effectively detect a large proportion of neonates with sepsis, reducing the risk of missed diagnoses. Specificity refers to the ability of a diagnostic test to correctly identify individuals without the condition. In the context of neonatal sepsis, a highly specific test would accurately identify those who do not have sepsis, minimizing the risk of false positives. False positives can lead to unnecessary treatment, which can be harmful to neonates and contribute to the development of antibiotic resistance. PCT has also demonstrated high specificity in studies evaluating its diagnostic accuracy for neonatal sepsis. The meta-analysis discussed here reports a pooled specificity of 0.82, suggesting that PCT can accurately identify those without sepsis and minimize false positives. The superior accuracy of PCT compared to other biomarkers, such as IL-6 and CRP, may be attributed to its unique biological properties. The rapid and specific response of PCT to bacterial infections makes it a reliable indicator of sepsis. Unlike other inflammatory markers that can be elevated in various conditions, PCT levels are less influenced by non-infectious inflammatory stimuli. This specificity helps to minimize false positives and unnecessary treatment, which is particularly important in neonates who are susceptible to the adverse effects of antibiotics. Neonatal sepsis, a severe systemic infection in newborns, remains a significant cause of morbidity and mortality worldwide. The condition's nonspecific clinical presentation often mimics other neonatal conditions, making early diagnosis challenging. Traditional diagnostic markers, such as white blood cell count and immature-to-total neutrophil ratio, often lack sensitivity and specificity, potentially leading to delayed treatment and adverse outcomes. Procalcitonin (PCT) has emerged as a valuable tool in the clinical management of neonatal sepsis. Its high diagnostic accuracy, rapid response to bacterial infections, and ability to guide clinical decision-making have the potential to revolutionize the care of newborns with suspected sepsis. Neonatal sepsis is a leading cause of morbidity and mortality in newborns, particularly in preterm and low birth weight infants. The early stages of sepsis can be subtle and nonspecific, making it challenging to distinguish from other neonatal conditions. Delays in diagnosis and

treatment can lead to rapid deterioration, with the potential for serious complications such as septic shock, meningitis, and multiple organ failure. PCT, with its rapid response to bacterial infections and high diagnostic accuracy, can facilitate early identification of neonates with sepsis. This early identification allows for prompt initiation of appropriate antibiotic therapy and supportive care, which can significantly improve outcomes and reduce the risk of mortality and morbidity. By accurately identifying neonates with sepsis, PCT can help to avoid unnecessary antibiotic treatment in those without the condition. This can shorten the duration of antibiotic exposure, reducing the risk of antibiotic resistance and adverse effects. Early diagnosis and treatment can lead to faster recovery and shorter hospital stays, minimizing the disruption to the newborn and family. Early and effective management of neonatal sepsis can reduce the risk of long-term complications, such as neurodevelopmental impairment and chronic health conditions. The overuse of antibiotics is a major public health concern, contributing to the development of antibiotic resistance and disrupting the delicate balance of the microbiome. In neonates, unnecessary antibiotic exposure can have additional adverse effects, such as increased risk of necrotizing enterocolitis and late-onset sepsis. The high specificity of PCT can help to avoid unnecessary antibiotic treatment in neonates without sepsis. By accurately identifying those who do not have the condition, PCT can guide clinicians in making informed decisions about antibiotic therapy. his can help to reduce the overall use of antibiotics in the neonatal population, minimizing the risk of antibiotic resistance and adverse effects. Neonatal intensive care units (NICUs) are often resource-constrained environments, with limited staff and equipment. The early identification of neonates with sepsis can help to prioritize resources and ensure that those who need the most intensive care receive it promptly. PCT can aid in this process by providing an objective measure of sepsis risk. Neonates with elevated PCT levels can be prioritized for further evaluation and treatment, while those with low PCT levels may be safely monitored with less intensive interventions. This can help to optimize resource allocation and ensure that all neonates receive the appropriate level of care. The integration of PCT into clinical algorithms and pathways can further enhance its impact on the management of neonatal sepsis. Several studies have explored the use of PCT-guided algorithms for the diagnosis and treatment of neonatal sepsis, with promising results. PCT is measured in neonates with suspected sepsis. Neonates are stratified into low-, intermediate-, and high-risk groups based on their PCT levels and other clinical factors. Management strategies are tailored to the risk level, with low-risk neonates potentially avoiding antibiotics and high-risk neonates receiving prompt and aggressive treatment. By accurately identifying neonates who do not require antibiotics, PCT-guided algorithms can significantly reduce antibiotic exposure. Early and targeted treatment guided by PCT can lead to better outcomes, including reduced mortality and morbidity. PCT-guided algorithms can help to prioritize resources and ensure that neonates with sepsis receive timely and appropriate care.[11-13]

Interleukin-6 (IL-6) is a cytokine, a type of signaling molecule that plays a crucial role in the immune system. It is produced by various cells, including immune cells and endothelial cells, in response to infection or inflammation. IL-6 is involved in a wide range of immune responses, including the activation of immune cells, the production of acute-phase proteins, and the regulation of inflammation. In the context of neonatal sepsis, IL-6 has been investigated as a potential diagnostic marker. Its levels are often elevated in neonates with sepsis, making it a potentially useful tool for early identification of the condition. IL-6 is a pleiotropic cytokine, meaning it has a wide range of biological activities. In the immune system, IL-6 plays a key role in both innate and adaptive immunity. Innate immunity is the body's first line of defense against infection. IL-6 activates various immune cells, including neutrophils, macrophages, and natural killer cells, to fight infection. IL-6 stimulates the liver to produce acute-phase proteins,

such as C-reactive protein (CRP), which are involved in the inflammatory response. IL-6 acts on the hypothalamus to induce fever, which can help to inhibit the growth of pathogens. Adaptive immunity is the body's specific defense against particular pathogens. IL-6 helps B cells to differentiate into plasma cells, which produce antibodies to fight infection. IL-6 influences the differentiation of T cells into different subtypes, which have various roles in the immune response. In neonatal sepsis, the immune system is activated in response to the invading pathogen. This activation leads to the production of various cytokines, including IL-6. IL-6 levels are often elevated in neonates with sepsis, and the degree of elevation may correlate with the severity of the infection. This makes IL-6 a potentially useful marker for early identification of sepsis and for monitoring the response to treatment. IL-6 is an early responder in the inflammatory cascade, and its levels may rise before other markers, such as PCT, become detectable. This makes it particularly useful for early identification of sepsis. IL-6 can be measured in various body fluids, including blood and cerebrospinal fluid, making it accessible in different clinical settings. IL-6 assays are generally less expensive than PCT assays, making them more affordable in resource-constrained settings. IL-6 can be elevated in various conditions besides sepsis, such as respiratory distress syndrome and perinatal asphyxia. This can lead to false positives and complicate interpretation of results. IL-6 levels can vary depending on the gestational age and postnatal age of the neonate, as well as the presence of other comorbidities. This can make it challenging to establish universal thresholds for diagnosis. Interleukin-6 (IL-6), a cytokine with a multifaceted role in the immune system, has garnered attention as a potential biomarker for neonatal sepsis. Its diagnostic accuracy has been the subject of numerous studies, and the meta-analysis discussed here further supports its potential value in the early identification of this critical condition. Sensitivity, a key measure of diagnostic accuracy, refers to the ability of a test to correctly identify individuals with the condition. In the context of neonatal sepsis, a highly sensitive test would accurately detect a large proportion of neonates who have the condition, minimizing the risk of false negatives. False negatives can be particularly detrimental in neonatal sepsis, as delayed treatment can lead to serious complications and even death. IL-6 has demonstrated good sensitivity in studies evaluating its diagnostic accuracy for neonatal sepsis. The meta-analysis discussed here reports a pooled sensitivity of 0.78, indicating that IL-6 can effectively detect a significant proportion of neonates with sepsis. Specificity, another crucial measure of diagnostic accuracy, refers to the ability of a test to correctly identify individuals without the condition. In the context of neonatal sepsis, a highly specific test would accurately identify those who do not have sepsis, minimizing the risk of false positives. False positives can lead to unnecessary treatment, which can be harmful to neonates and contribute to the development of antibiotic resistance. IL-6 has also demonstrated good specificity in studies evaluating its diagnostic accuracy for neonatal sepsis. The meta-analysis discussed here reports a pooled specificity of 0.75, suggesting that IL-6 can effectively minimize false positives. While IL-6 showed slightly lower accuracy compared to PCT in this meta-analysis, it may still have a valuable role in certain clinical scenarios. For instance, IL-6 may be particularly useful in the early stages of sepsis when PCT levels may not yet be significantly elevated. This is because IL-6 is an early responder in the inflammatory cascade, and its levels may rise before PCT becomes detectable. It is important to note that IL-6 levels can be influenced by various factors, including gestational age, postnatal age, and the presence of other comorbidities. This can make it challenging to establish universal thresholds for diagnosis. While research is ongoing, its promising diagnostic accuracy and rapid response to infection suggest that IL-6 could be a valuable tool for early identification of neonates at risk, enabling prompt intervention and potentially improving outcomes. Neonatal sepsis is a leading cause of morbidity and mortality in newborns,

particularly in preterm and low birth weight infants. The early stages of sepsis can be subtle and nonspecific, making it challenging to distinguish from other neonatal conditions. Delays in diagnosis and treatment can lead to rapid deterioration, with the potential for serious complications such as septic shock, meningitis, and multiple organ failure. IL-6, with its rapid response to infection, could play a crucial role in the early identification of neonates with sepsis. Its levels often rise before other markers, such as PCT, making it a particularly valuable tool in the early stages of the disease. Incorporating IL-6 into clinical algorithms and pathways could enhance risk stratification and guide clinical decision-making. For instance, in neonates with suspected sepsis, an elevated IL-6 level could prompt further investigation and closer monitoring, even if other markers are not yet suggestive of sepsis. IL-6 could be used in conjunction with other clinical and laboratory findings to guide clinical decision-making. This could include additional laboratory tests, such as blood cultures and inflammatory markers, as well as imaging studies to identify the source of infection. Neonates with elevated IL-6 levels may require closer monitoring of their vital signs, oxygen saturation, and other clinical parameters. In some cases, an elevated IL-6 level may warrant early intervention, such as empirical antibiotic therapy, even before a definitive diagnosis of sepsis is established. Early identification and intervention could improve outcomes and reduce the risk of complications and death. IL-6 could help to identify neonates who do not require antibiotics, reducing the risk of antibiotic resistance and adverse effects. IL-6 could help to prioritize resources and ensure that neonates with sepsis receive timely and appropriate care.[14-17]

C-reactive protein (CRP) is an acute-phase protein produced by the liver in response to inflammation. It has been widely used as a marker of infection and inflammation in various clinical settings, including neonatology. However, in the context of neonatal sepsis, CRP has shown limitations in its diagnostic accuracy compared to newer biomarkers such as procalcitonin (PCT) and interleukin-6 (IL-6). Sensitivity, a key measure of diagnostic accuracy, refers to the ability of a test to correctly identify individuals with the condition. In the context of neonatal sepsis, a highly sensitive test would accurately detect a large proportion of neonates who have the condition, minimizing the risk of false negatives. False negatives can be particularly detrimental in neonatal sepsis, as delayed treatment can lead to serious complications and even death. CRP, unfortunately, has not demonstrated high sensitivity in studies evaluating its diagnostic accuracy for neonatal sepsis. The meta-analysis discussed here reports a pooled sensitivity of 0.70, indicating that CRP misses a significant proportion of neonates with sepsis. This high false-negative rate raises concerns about its reliability as a standalone marker for early identification of neonatal sepsis. Specificity, another crucial measure of diagnostic accuracy, refers to the ability of a test to correctly identify individuals without the condition. In the context of neonatal sepsis, a highly specific test would accurately identify those who do not have sepsis, minimizing the risk of false positives. False positives can lead to unnecessary treatment, which can be harmful to neonates and contribute to the development of antibiotic resistance. CRP has also shown limitations in its specificity for neonatal sepsis. The meta-analysis discussed here reports a pooled specificity of 0.68, suggesting that CRP can lead to a considerable number of false positives. This means that a significant proportion of neonates without sepsis may be incorrectly identified as having the condition, potentially leading to unnecessary treatment and interventions. CRP levels rise in response to various inflammatory stimuli, not just bacterial infections. This can lead to false positives in neonates with non-infectious inflammatory conditions, such as respiratory distress syndrome or perinatal asphyxia. CRP levels may rise more slowly than PCT or IL-6 in the early stages of sepsis, potentially delaying diagnosis. This delayed response can be problematic in neonatal sepsis, as early

intervention is crucial for improving outcomes. Maternal CRP can cross the placenta and influence neonatal CRP levels, particularly in the first few days of life. This can make it challenging to interpret CRP results in newborns. C-reactive protein (CRP), a well-established marker of inflammation, has been widely used in various clinical settings, including neonatology. However, when it comes to diagnosing neonatal sepsis, a serious and potentially life-threatening condition, CRP exhibits limitations in its accuracy compared to newer biomarkers like procalcitonin (PCT) and interleukin-6 (IL-6). Understanding the factors contributing to CRP's lower accuracy in neonatal sepsis is crucial for clinicians to interpret its results appropriately and make informed decisions about diagnosis and treatment. One of the primary limitations of CRP in diagnosing neonatal sepsis is its non-specificity. CRP levels rise in response to a wide range of inflammatory stimuli, not just bacterial infections. This means that various conditions, both infectious and non-infectious, can trigger an increase in CRP levels. In neonates, this non-specificity can be particularly problematic. Newborns often experience various physiological stressors around the time of birth, such as hypoxia (lack of oxygen) and tissue injury, which can trigger an inflammatory response and elevate CRP levels. Additionally, neonates may have underlying conditions, such as respiratory distress syndrome or meconium aspiration syndrome, that can also cause inflammation and increase CRP levels. This lack of specificity makes it challenging to differentiate between infectious and non-infectious causes of inflammation based on CRP alone. An elevated CRP level in a neonate could indicate a bacterial infection, but it could also be due to a non-infectious inflammatory condition. This ambiguity can lead to false positives, where neonates without sepsis are incorrectly diagnosed with the condition, potentially leading to unnecessary antibiotic treatment and interventions. Another factor contributing to CRP's lower accuracy in neonatal sepsis is its delayed response. CRP levels typically rise within 6-12 hours after the onset of inflammation, but they may not peak until 24-48 hours later. This delayed response can be problematic in neonatal sepsis, where early intervention is crucial for improving outcomes. In the critical early stages of sepsis, when prompt treatment is essential, CRP levels may not yet be significantly elevated. This can lead to a missed or delayed diagnosis, as clinicians may rely on CRP as an initial indicator of infection. By the time CRP levels become significantly elevated, the infection may have progressed, potentially leading to more severe complications and poorer outcomes. This delayed response is particularly concerning in neonates, as their immune systems are immature and they are more susceptible to rapid deterioration from sepsis. Early diagnosis and treatment are essential to prevent serious complications and improve survival rates. Maternal CRP can cross the placenta and influence neonatal CRP levels, particularly in the first few days of life. This can make it challenging to interpret CRP results in newborns. If the mother has an elevated CRP level due to an infection or other inflammatory condition, the neonate's CRP level may also be elevated, even if the neonate does not have an infection. This can lead to false positives and unnecessary interventions. Conversely, if the mother has a low CRP level, the neonate's CRP level may also be low, even if the neonate has an infection. This can lead to false negatives and delayed diagnosis. The influence of maternal CRP is particularly pronounced in preterm infants, as their immature livers may not be able to clear CRP as efficiently as term infants. This can further complicate the interpretation of CRP levels in this vulnerable population. C-reactive protein (CRP), a long-standing marker of inflammation, has been a mainstay in the evaluation of various infectious and inflammatory conditions. While its limitations in diagnosing neonatal sepsis are acknowledged, CRP can still play a valuable role in the clinical management of this condition, particularly when used in conjunction with other clinical and laboratory findings. CRP's primary role in neonatal sepsis management lies in its ability to serve as an adjunctive

marker for diagnosis. While not recommended as a standalone diagnostic tool due to its lower sensitivity and specificity compared to newer biomarkers like PCT and IL-6, CRP can provide supportive evidence when clinical signs and symptoms suggest the possibility of sepsis. In neonates with suspected sepsis, an elevated CRP level, along with clinical findings such as fever, respiratory distress, or lethargy, can strengthen the suspicion of infection and prompt further investigation. This may include additional laboratory tests, such as blood cultures and other inflammatory markers, as well as imaging studies to identify the source of infection. CRP can also be a useful tool for monitoring the response to treatment in neonates with confirmed sepsis. Serial CRP measurements can provide valuable information about the trajectory of the infection and the effectiveness of the chosen treatment strategy. Decreasing CRP levels over time may indicate a favorable response to therapy. This suggests that the infection is being controlled and the inflammatory response is subsiding. Persistently elevated or rising CRP levels, despite appropriate treatment, could suggest treatment failure or the development of complications. This may warrant a reevaluation of the treatment plan, including consideration of alternative antibiotics or additional supportive care measures. To maximize the utility of CRP in neonatal sepsis management, it is essential to integrate it into comprehensive clinical pathways. These pathways should incorporate clinical findings, laboratory tests (including CRP and other biomarkers), and imaging studies to guide clinical decision-making. By incorporating CRP into a broader clinical context, clinicians can interpret its results more accurately and avoid unnecessary interventions based on isolated CRP elevations. This integrated approach can help to ensure that neonates with sepsis receive timely and appropriate treatment while minimizing unnecessary antibiotic exposure.[18-20]

4. Conclusion

This meta-analysis indicates that PCT and IL-6 hold promise as valuable adjuncts to traditional diagnostic methods for neonatal sepsis. Of the three biomarkers evaluated, procalcitonin (PCT) demonstrated the highest diagnostic accuracy for neonatal sepsis, followed by interleukin-6 (IL-6). C-reactive protein (CRP) exhibited the lowest accuracy. However, further large-scale prospective studies are needed to validate these findings. Future research should focus on larger-scale prospective studies, head-to-head comparisons of PCT, IL-6, and other biomarkers, the development of clinical prediction rules incorporating these biomarkers, and cost-effectiveness analyses.

5. References

1. Abdel-Hakim G, Shehata N, Abdel-Hameed W, Abdel- Wahab N. Cord blood interleukin-6 as a predictor of early onset sepsis in high risk neonates. Ann Neonatol J. 2019; 1(2): 38–48.
2. Ebenebe CU, Hesse F, Blohm ME, Jung R, Kunzmann S, Singer D. Diagnostic accuracy of interleukin-6 for early-onset sepsis in preterm neonates. J Matern Fetal Neonatal Med. 2021; 34(2): 253–8.
3. Hahn W-H, Song J-H, Kim H, Park S. Is procalcitonin to C-reactive protein ratio useful for the detection of late onset neonatal sepsis? J Matern Fetal Neonatal Med. 2018; 31(6): 822–6.
4. Borges J, Hospital De Santa Maria. Early neonatal sepsis screening: Procalcitonin and C-reactive protein diagnostic value. Neonatol Clin Pediatr. 2020; 7(3): 1–5.
5. Yadav S, Sharif M, Saxena A, Kolhe S, Dhole D. Role of Procalcitonin and C-Reactive Protein in the early diagnosis of neonatal sepsis. Indian J Neonatal Med Res. 2021.
6. Chaurasia S, Anand P, Sharma A, Nangia S, Sivam A, Jain K, et al. Procalcitonin for detecting culture-positive sepsis in neonates: a prospective, multicenter study. Neonatology. 2023; 120(5): 642–51.
7. Goyal S, Sharma CM, Kumar R, Mohan N. Platelet count and its indices as diagnostic

markers of neonatal sepsis: a cross-sectional study. Int J Contemp Pediatr. 2024; 11(7): 951–6.

8. Regassa DA, Nagaash RS, Habtu BF, Haile WB. Diagnostic significance of complete blood cell count and hemogram-derived markers for neonatal sepsis at Southwest Public Hospitals, Ethiopia. World J Clin Pediatr. 2024; 13(2): 92392.
9. O'Neil M, Demeulenaere SK, DeChristopher PJ, Holthaus E, Jeske W, Glynn L, et al. Syndecan-1 level, a marker of endothelial glycocalyx degradation, is associated with fetal exposure to chorioamnionitis and is a potential biomarker for early-onset neonatal sepsis. Pediatr Dev Pathol. 2024; 27(4): 318–26.
10. Khedr D, Nabil S, Abdelnaby A, Abdulrazek AA, Lotfy S. The C-reactive protein/albumin ratio as an early diagnostic marker of neonatal sepsis in preterm neonates: a case-control study. Pediatr Sci J. 2024; 4(2): 103–10.
11. Suman P, Kulkarni N, Ukkali SB, Thobbi AN. Unveiling neonatal risk factors, clinical profile and early diagnostic markers of neonatal sepsis in a tertiary care hospital from South India: a cross-sectional study. Int J Contemp Pediatr. 2024; 11(8): 1038–43.
12. Zhu S, Zhou Q, Hu Z, Jiang J. Assessment of neutrophil to lymphocyte ratio, platelet to lymphocyte ratio and systemic immune-inflammatory index, as diagnostic markers for neonatal sepsis. J Int Med Res. 2024; 52(8): 3000605241270696.
13. Ahac F. Nursing interventions and biochemical markers in early detection of neonatal sepsis. Egypt J Chem. 2024.
14. Lee SYR, Leung CW. Histological chorioamnionitis - implication for bacterial colonization, laboratory markers of infection, and early onset sepsis in very-low-birth-weight neonates. J Matern Fetal Neonatal Med. 2012; 25(4): 364–8.
15. El Shimi MS, Abou Shady NM, Hamed GM, Shedeed NS. Significance of neutrophilic CD64 as an early marker for detection of neonatal sepsis and prediction of disease outcome. J Matern Fetal Neonatal Med. 2017; 30(14): 1709–14.
16. Raghav A, Kumar A, Anand P, Yadav G, Gera R. Significance of serum inflammatory markers in predicting bacterial meningitis amongst neonates with sepsis. Indian J Neonatal Med Res. 2021.
17. Hashem HE, Ibrahim ZH, Ahmed WO. Diagnostic, prognostic, predictive, and monitoring role of neutrophil CD11b and monocyte CD14 in neonatal sepsis. Dis Markers. 2021; 2021: 4537760.
18. Vázquez Rodríguez S, Arriaga Pizano LA, Laresgoiti Servitje E, Mancilla Ramirez J, Peralta Méndez OL, Villalobos Alcazar G, et al. Multiparameter flow cytometry analysis of leukocyte markers for diagnosis in preterm neonatal sepsis. J Matern Fetal Neonatal Med. 2021; 34(14): 2323–33.
19. Gururaju D, Parameshwarappa NN, Rao AH, Rangappa M. Diagnostic accuracy of platelet indices as a marker for sepsis in neonates: a case-control study. Indian J Neonatal Med Res. 2022.
20. Smith J, Alcock G, Monk B NNP, Jones ER. Core and peripheral temperature as a marker for sepsis in the preterm infant. J Neonatal Nurs. 2022; 28(5): 340–3.